Total Syntheses of PI-201 and Related Compounds

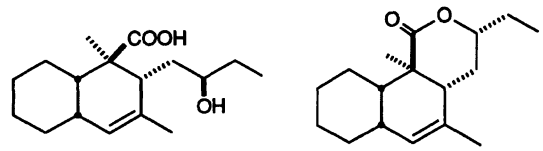
Takeshi Murata, Toshihito Kumagai, Makoto Ishikawa, Kin-ichi Tadano,* and Seiichiro Ogawa

Department of Applied Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223

(Received June 24, 1996)

The thermal intramolecular Diels–Alder cycloaddition of a 2 : 1 mixture of ethyl (2*E*,8*E* and *Z*, 10*E*,13*R*)-13-(*t*-butyldimethylsilyl) oxy-2,10-dimethyl-2,8,10-pentadecatrienoate provided four diastereomeric cycloadducts. Deprotection of one of the cycloadducts provided PI-201, a novel platelet aggregation inhibitor, as its natural form. Three stereoisomers of PI-201 were prepared from the other cycloadducts. The intramolecular cycloadditions of some structurally similar trienes were also investigated.

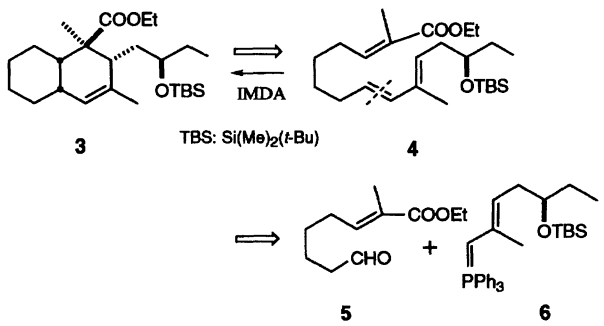
In 1992, the group of Taisho Pharmaceutical Co., Ltd. reported the isolation of new platelet aggregation inhibitors, designated as PI-201 (**1**) and PI-200 (**2**), from the fermentation broth of *Streptomyces* sp. A7498.[1] These two natural products, **1** and **2**, exhibit potent ADP-induced aggregation inhibitory activity against rabbit platelets with an IC_{50} of 7.1×10^{-4} M and 3.8×10^{-4} M, respectively (1 M = 1 mol dm^{-3}). The relative stereochemistry of **1** was fully elucidated by means of spectral analyses, and finally confirmed by a single-crystal X-ray analysis.[1] Compound **1** is a trisubstituted octahydronaphthalene carboxylic acid possessing four contiguous stereogenic centers, one of which carries a 2-hydroxybutyl group. The structure of another natural product **2**, the δ-lactone form of **1**,[2] was confirmed based on the spectral correlation to **1**. Herein we described in detail the total syntheses of **1** and some related compounds in enantio-enriched forms.[3] The present synthesis established the unsettled absolute stereochemistry of **1**, and thus that of **2**, as depicted in Fig. 1.



1 **2**

Fig. 1.

As depicted in Eq. 1, an octahydronaphthalene derivative **3**, a fully protected form of **1**, was expected to be constructed by the intramolecular Diels–Alder (IMDA) cycloaddition[4] of triene **4**. The substrate **4** would be prepared by the Wittig coupling of an ω-formyl-α,β-unsaturated ester **5** and an enantiomeric phosphorus ylide **6**. Our major concern was the stereoselectivity (π-facial- and diastereoselectivity) in the IMDA cycloaddition of the triene **4**.



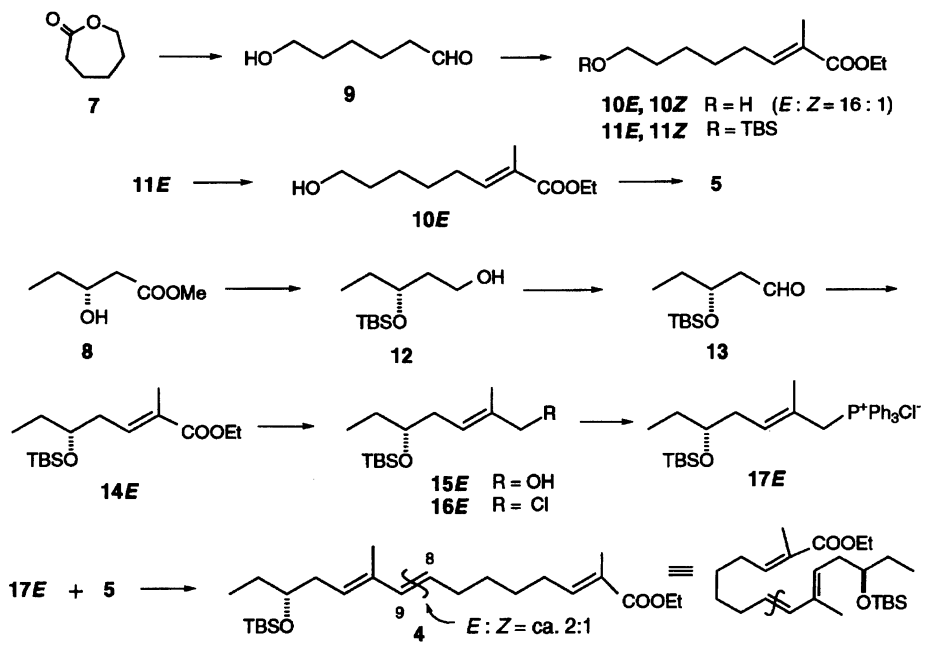
3 **4** **5** **6**

(1)

Results and Discussion

Two coupling partners, **5** and **6**, were prepared straightforwardly from ε-caprolactone (6-hexanolide) (**7**) and enantioenriched methyl (*R*)-3-hydroxypentanoate (**8**), donated by Kaneka Co., Ltd. (>95% ee),[5] respectively (Scheme 1). Diisobutylaluminum hydride (Dibal-H) reduction of **7**, followed by Wittig olefination of crude ω-hydroxy aldehyde **9** with Ph_3P=C(Me)COOEt in refluxing benzene, afforded an inseparable mixture of α,β-unsaturated esters, **10*E*** and **10*Z***, in a combined yield of 61% from **7**. Protection of the hydroxyl groups in the mixture as *t*-butyldimethylsilyl (TBS) ethers gave a mixture of **11*E*** and **11*Z***. At this stage, the mixture could be cleanly separated by repeated silica-gel chromatography, isolating **11*E*** (79%) and **11*Z*** (5%). The major (*E*)-isomer **11*E*** was desilylated with tetrabutylammonium fluoride (TBAF) to give geometrically homogeneous **10*E*** (93%). Pyridinium chlorochromate (PCC) oxidation of **10*E*** gave the Wittig coupling partner **5**.

Another coupling partner, a phosphonium salt **17*E***, was prepared as follows. Compound **8** was converted into known (*R*)-3-*O*-(*t*-butyldimethylsilyl)oxy-1-pentanol (**12**) according to a reported procedure.[6] The PCC oxidation of **12**, and a subsequent Wittig reaction of the resulting aldehyde **13** with Ph_3P=C(Me)COOEt, gave α,β-unsaturated ester **14*E***, which was contaminated by less than 5% (^{1}H NMR analysis) of the (*Z*)-isomer **14*Z***, in a combined yield of 76%. Dibal-H reduction of **14*E*** gave allylic alcohol **15*E*** in 81% yield. Allylic chlorination of **15*E*** with Ph_3P and CCl_4 gave the allyl chloride **16*E*** in 65% yield. Heating **16*E*** with Ph_3P (neat) at



Scheme 1.

70—80 °C for 3 d provided the triphenylphosphonium chloride **17*E***. This salt consist of the (*E*)-isomer predominantly (*E* : Z=>20 : 1, ^{1}H NMR analysis), was directly used for the next Wittig coupling. The treatment of the phosphonium salt **17*E*** with *n*-BuLi in THF gave the ylide **6**. To a solution of **6** in THF was added aldehyde **5**. The mixture was briefly stirred at room temperature (r.t.) to give the desired triene **4** as an inseparable (*E* : *Z*) mixture on C8–C9 in 61% yield. Although the ratio of the (*E*)- and (*Z*)-isomers on C8–C9 was estimated to be 2 : 1 (based on the ^{1}H NMR analysis), they were used for IMDA cycloaddition due to a difficulty in their separation.

First, the IMDA cycloaddition of the substrate **4** was examined under two Lewis acid-catalyzed conditions, i.e., (1) Et_2AlCl/CH_2Cl_2/−15 °C to r.t., (2) $EtAlCl_2/CH_2Cl_2$/−15 °C to r.t., or under high-pressure conditions (11000 atm/CH_2Cl_2/r.t./20 h). Neither conditions provided the desired cycloadduct(s). The trienoic ester **4** was recovered almost quantitatively in all cases. Fortunately, IMDA cycloaddition took place under thermal conditions by heating a toluene solution of **4** (0.11 mmol ml^{-1}) in a sealed tube at 200 °C for 27 h. A ^{1}H NMR inspection of the reaction mixture revealed that four cycloadducts **18**—**20** and **3** (Fig. 2) were produced without specified diastereoselectivity. Purification of the mixture by silica-gel chromatography finally gave two homogeneous *trans*-fused cycloadducts, **18** and **19**, in 15 and 14% yields, respectively. Also, an inseparable mixture of two *cis*-fused cycloadducts, **20** and **3**, was isolated in a combined yield of 24%. An uncyclized product **21** was isolated from the mixture in approximately 20% yield, which could not be completely separated from unreacted trienes, **4*E*** and **4*Z*** (<10% based on ^{1}H NMR analysis).

The structure of **21** was determined by a ^{1}H NMR analysis, including NOE difference experiments, as shown in Fig. 2. Compound **21** was supposed to be formed from the (*Z*)-

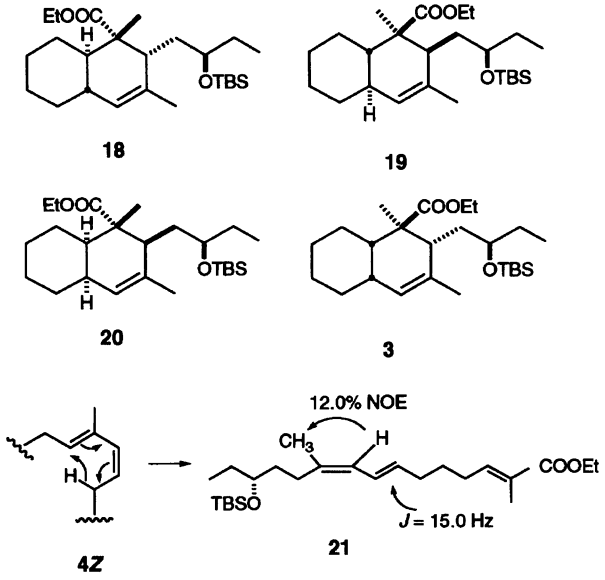


Fig. 2.

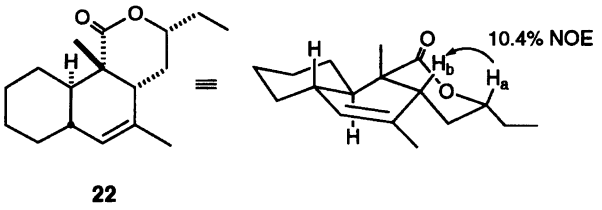
isomer of **4** through a thermal 1,5-hydrogen shift, as depicted in Fig. 2.

The structural assignment of each cycloadduct was achieved as follows. Simultaneous deprotection of both the silyl group and the ethyl ester in **18** was achieved by stirring a solution of **18** in DMSO with potassium *t*-butoxide at 60 °C followed by acidification of the solution with HCl (pH 3).[7] In the case of **18**, δ-lactone **22** was obtained in 92% yield as a consequence of lactonization of the intermediary δ-hydroxy carboxylic acid. The structure of **22**, and therefore that of **18**, was established by an examination of its ^{1}H NMR, including an NOE difference experiment, as shown in Fig. 3. A 10.4% enhancement of the angular proton H_b was observed when H_a was irradiated.

Deprotection of another *trans*-cycloadduct **19** under the same reaction conditions as that used for **18** provided carboxylic acid **23** in 94% yield (Fig. 4). In this case, the corresponding δ-lactone **24** was obtained by stirring **23** in a 1 M HCl solution at 40 °C. The structure of **24**, and therefore those of **19** and **23**, was determined by a ^{1}H NMR analysis, including an NOE difference experiment, as shown in Fig. 4. Compound **24** did not show any NOE enhancement between H_a and H_b.

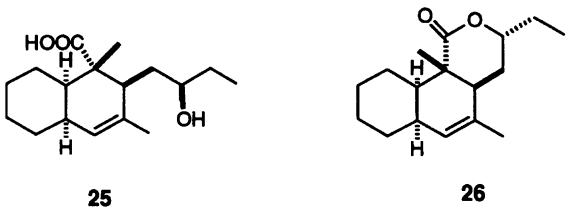
Under the same deprotection conditions, the inseparable mixture of **20** and **3** was converted into carboxylic acids, **25** and **1**, which were partially separated by chromatography on silica gel, giving **25** (25%), **1** (28%), and a mixture (28%). (Fig. 5). The synthetic **1** was identical to a natural specimen based on a direct comparison (TLC, ^{1}H NMR, and MS). Also, the levorotatory property of the synthetic **1** concluded the absolute stereochemistry of natural **1** to be that depicted in Fig. 1. A treatment of **25** with *p*-TsOH provided the corresponding δ-lactone **26** in 77% yield.

The structural relationship between two *trans*-fused cycloadducts, **18** and **19**, was further correlated by the following experiments. Both δ-lactones **22** and **24** were reduced with $LiAlH_4$ to provide diols **27** and **30** (Scheme 2). Selective protection of the primary hydroxy groups in **27** and **30** as the



22

Fig. 3.



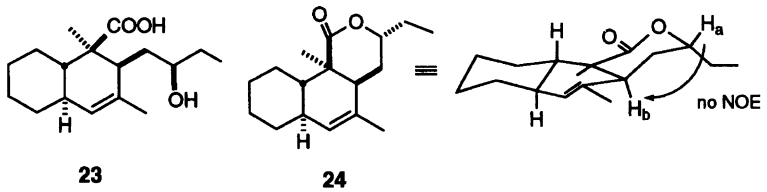
25 **26**

Fig. 5.

corresponding TBS ethers gave the silyl ethers **28** and **31**. PDC oxidation of **28** and **31** gave **29** and **32**. Ketones **29** and **32** are a pair of enantiomers, of which the spectral data (^{1}H NMR, IR, and MS) were completely identical, and the optical rotations of **29** and **32** showed the same magnitude, but were opposite in sign. These results established the enantiomeric relationship of the octahydronaphthalene nuclues in **18** and **19**.

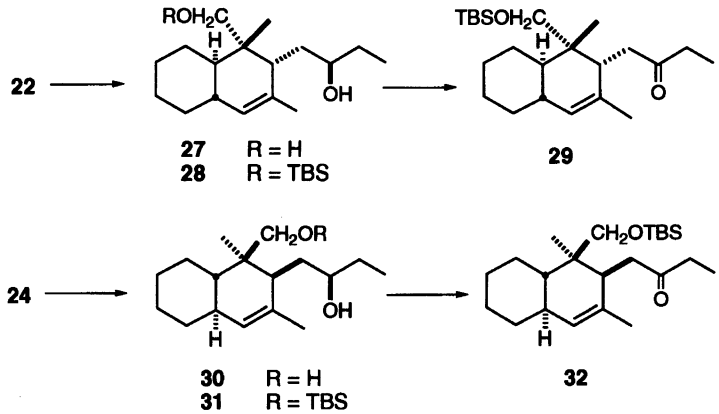
We also confirmed the enantiomeric relationship of the bicyclic nucleus in **20** and **3**. The desilylation of an inseparable mixture of **20** and **3** under acidic conditions gave an inseparable mixture of **33** and **34** (Scheme 3). PDC oxidation of a mixture of **33** and **34** gave solely a racemic mixture of two ketones, **35** and **36**.

In order to obtain more insight concerning the stereoselectivity in the IMDA cycloaddition of **4**, we next investigated the IMDA cycloadditions of two structurally similar substrates, **38** and **45**. The preparation of α,β-unsaturated aldehyde **38** was carried out from the trienoic ester **4** (Scheme 4). The Dibal-H reduction of the 2 : 1 (*E*/*Z*)-mixture **4** afforded alcohols **37**, which were oxidized with $BaMnO_4$ to give **38** as a 2 : 1 geometrical mixture in 83% yield from **4**. In contrast to the case of **4**, the IMDA cycloaddition of **38** proceeded smoothly under Lewis acid-promoted condi-

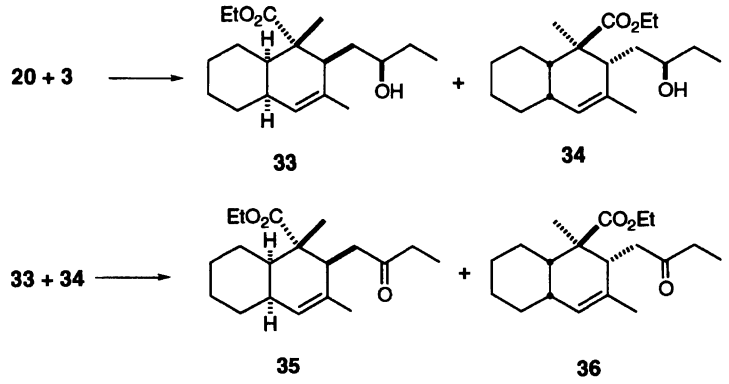


23 **24**

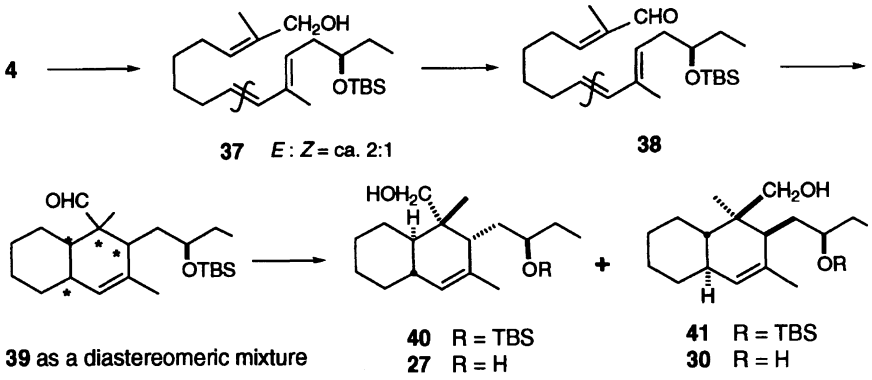
Fig. 4.



Scheme 2.



Scheme 3.

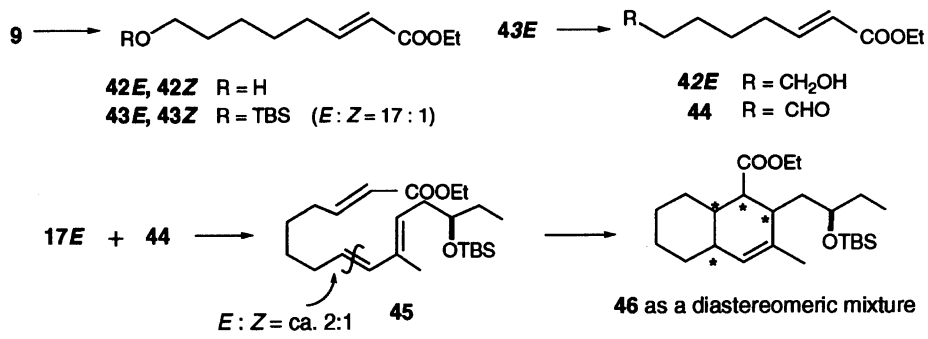


Scheme 4.

tions. When **38** was treated with Et_2AlCl (3.0 mol amt.) in CH_2Cl_2 at −18 °C, an inseparable mixture **39** of four cycloadducts was obtained, in which two isomers were predominant. Based on a ^1H NMR analysis of the mixture, the ratio of the diastereomeric mixture **39** was approximately 10 : 10 : 1 : 1. The mixture **39** was obtained in a combined yield of 50%. Under these conditions, unreacted (*Z*)-isomer **38*Z*** was recovered in 29% yield without a 1,5-hydrogen shift, which was observed in the case of a thermal IMDA reaction of **4**. The structures of the two predominant cycloadducts were confirmed by derivatization of the mixture **39** into structurally defined diols, **27** and **30**, via **40** and **41** [(1) $LiAlH_4$/THF; (2) AcOH : H_2O : THF=3 : 1 : 1]. The intermediates, **40** and **41**, were cleanly separated by chromatography on silica gel. Although the yield was unsatisfactory (20%), the same two *endo*-cycloadducts (ca. 1 : 1) were also obtained by a treatment of **38** with $Et_2O{\cdot}BF_3$ (1 mol amt.) in CH_2Cl_2 at −78 °C. Consequently, it is obvious that the general *endo*-preferential cyclization mode governs the IMDA reaction of **38** under the Lewis acid-promoted conditions, which gave two *trans*-fused octahydronaphthalene derivatives predominantly.

Next, we investigated the IMDA cycloaddition of trienoic ester **45** carrying an acrylic ester part as a dienophile in place of the methacrylic ester part in **4**. The preparation of **45** was commenced with **9** (Scheme 5). Wittig olefination of **9** with Ph_3P=CHCOOEt gave unsaturated esters **42*E*** and **42*Z*** in predominance of the (*E*)-isomer (*E* : *Z*=17 : 1). These geometrical isomers were separated after silylation of the mixture. The (*E*)-isomer of the corresponding silyl ether **43*E*** was then desilylated to give pure **42*E***. PCC oxidation of **42*E*** gave aldehyde **44**. A Wittig coupling of **6** (via **17*E***) and **44** provided the triene **45** as a 2 : 1 mixture of the geometrical isomers on the newly introduced double bond in a combined yield of 58% from **42*E***. Under the Lewis acid (Et_2AlCl)-promoted conditions successfully used for the substrate **38**, the IMDA cycloaddition of **45** essentially did not proceed. The starting mixture **45** was recovered intact. An IMDA cycloaddition was only achieved when the substrate **45** was heated in toluene at 160 °C (sealed tube) for 21 h. After chromatographic purification of the reaction mixture on silica gel, an inseparable mixture of four cycloadducts **46** was obtained in a combined yield of 60%. The unreacted (*Z*)-isomer **45*Z*** was recovered in a 17% yield. The ratio of the mixture was determined to be 2 : 2 : 1 : 1 by a ^1H NMR spectral analysis. Owing to this less satisfactory stereoselectivity observed in the case of the IMDA cycloaddition of **45**, and also due to the difficulty in a clean separation of the cycloadduct mixture **46**, we did not pursue the stereochemical assignment of each cycloadduct in the mixture.

For interpreting the stereochemical outcomes observed in the IMDA cycloadditions of the substrates, **4**, **38**, and **45**, we consider the following comments. In all cases, no specified π-facial selectivity, i.e., the approach of the dienophile part from the upper or lower side of the diene plane, was observed. These non-stereoselectivities suggest that the functional groups on the diene parts and those on the trisubstituted (for **4** and **38**) or disubstituted (for **45**) dienophile parts do



Scheme 5.

not interfere unfavorably with each other in their transition state of the cycloaddition. In addition, no or a least (if any) steric hindrance of the bulky *t*-butydimethylsilyl ether group in the diene part participates in the stereochemical bias of these cycloadditions. Only in the case of **38** was a high *endo*/*exo* ratio observed under the Lewis acid-promoted conditions. Based on the HOMO–LUMO electronic environments previously calculated for a variety of IMAD cycloadditions, it can generally be said that *trans*-fused cycloadducts, being formed through *endo*-mode cyclization, are preferentially formed when activation (polarization) of the dienophile part is realized by introducing electron-withdrawing groups.[8] An aldehyde group seems to be the most directing group for the formation of *trans*-fused bicyclic compounds.[8] This tendency was the case for **38**. Recent arguments concerning IMDA cycloadditions also refer to the concept of "twist asynchronicity" and "*endo* stabilization of the transition state" (so-called the secondary orbital interaction), which account for the increased formation of the *trans*-fused cycloadducts.[8] However, this electron-withdrawing substituent effect was remarkably diminished in the thermal cycloadditions of **4** and **45**, both carrying an ester functionally as an activating group. Both substrates provided a mixture of cycloadducts without notable *endo*/*exo*-selectivity. Meanwhile, a slight, but apparent, improvement in the stereoselectivity was observed in the case of **45**, as compared with the case of the substrate **4** (2 : 2 : 1 : 1 vs. 1 : 1 : 1 : 1). Although we can not present a precise explanation for this difference in the stereochemical outcome observed using **4** and **45**, it is likely that the existence of an additional methyl group in **4** would decrease the polarization of the dienophile part, and also increase the steric congestion in the transition state. These factors may reduce the preferential proportion of particular conformation(s), such as for *endo*-mode cyclization in the transition state of the IMDA cycloaddition of **4**. Consequently, a variety of conformations may be probable in the transition state of the IMDA cycloaddition, leading to the formation of a mixture of the four cycloadducts, **18**—**20** and **3**, in a nearly identical ratio.

In summary, we achieved the total synthesis of a potent platelet aggregation inhibitor, PI-201 **1**, featuring the IMDA cycloaddition of enantiomerically enriched substrate **4** for the key octahydronaphthalene skeleton formation. The cycloaddition was proceeded only under thermal conditions. We could also find a high *endo*-selective IMDA cycloaddition of a structurally similar substrate **38** under Lewis acid-promoted conditions. On the other hand, another substrate **45** did not reveal any useful stereoselectivity under thermal IMDA cycloaddition conditions.

Experimental

Melting points are uncorrected. Specific rotations were measured using a JASCO Model 370 digital polarimeter in a 10 mm cell in a $CHCl_3$ solution. IR spectra were recorded using a JASCO IR-810 (neat) or BIO-RAD DEGILAB FTS-65 (KBr-disk) spectrometer. ^{1}H NMR spectra were recorded using a JEOL EX-90 (90 MHz) or JEOL GX-270 (270 MHz) spectrometer in a $CDCl_3$ solution with tetramethylsilane used as an internal standard. High-resolution mass spectra (HRMS) were taken using a Hitachi M-80 mass spectrometer.

Thin-layer chromatography (TLC) was performed with a glass plate-coated Kieselgel 60 GF_{254} (Merck). Crude reaction mixtures or extractive materials were chromatographed on silica-gel 60 K070 (Katayama Chemicals).

Unless otherwise specified, the reactions were carried out at room temperature (r.t.). The extractive solvent was dried over anhydrous Na_2SO_4. The reagents and solvents were removed by concentration in vacuo using an evaporator with a bath at 35—45 °C.

The solvents were dried (drying reagent in parenthesis) and distilled prior to use: tetrahydrofuran = THF ($LiAlH_4$, then Na/benzophenone ketyl), *N*,*N*-dimethylformamide = DMF ($MgSO_4$), CH_2Cl_2 (CaH_2), benzene (CaH_2), dimethyl sulfoxide = DMSO (CaH_2), pyridine (NaOH), and toluene (CaH_2).

Mixture of Ethyl (2*E* and *Z*)-8-Hydroxy-2-methyl-2-octenoate (10*E* and 10*Z*). The following reaction was carried out under Ar. To a cold (−78 °C) stirred solution of **7** (1.96 g, 17.1 mmol) in CH_2Cl_2 (50 ml) was added Dibal-H (1.5 M solution in toluene, 12.3 ml, 18.5 mmol) dropwise over a period of 40 min. After being stirred at −78 °C for 30 min, the solution was quenched with H_2O. The resulting gels were filtered off, and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo to give 2.03 g of crude **9**, which was used in the next step without purification, as a pale-yellow oil: TLC, R_f 0.29 (EtOAc/hexane, 1 : 1); ^{1}H NMR (90 MHz) δ = 1.40—1.93 (m, 7H), 2.38—2.58 (m, 2H), 3.65 (t, J = 6.0 Hz, 2H), 9.78 (t, J = 1.3 Hz, 1H).

To a stirred solution of crude **9** (2.03 g) in benzene (20 ml) was added $Ph_3P{=}C(Me)CO_2Et$ (6.49 g, 17.9 mmol). The solution was refluxed for 30 min, and the solvent was removed by evaporation. The residue was triturated with excess petroleum ether, and the precipitated $Ph_3P{=}O$ was removed by filtration and washed well with petroleum ether. The filtrate and washings were combined and

then concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 10 to 1 : 3) to give 2.09 g (61% from **7**) of an inseparable mixture of **10*E*** and **10*Z*** as a colorless oil (the geometric ratio of the isomers, *E* : *Z*=ca. 16 : 1, was determined by ^{1}H NMR analysis): TLC, R_f 0.58 (EtOAc/hexane, 1 : 1); ^{1}H NMR (270 MHz) δ=1.296 (t, *J*=7.1 Hz, 3H×16/17), 1.300 (t, *J*=7.1 Hz, 3H×1/17), 1.33—1.73 (m, 7H), 1.83 (dd, *J*=1.3 Hz, 3H×16/17), 1.89 (dd, *J*=1.5 Hz, 3H×1/17), 2.12—2.25 (m, 2H×16/17), 2.40—2.52 (m, 2H×1/17), 3.65 (t, *J*=6.4 Hz, 2H), 4.188 (q, *J*=7.1 Hz, 2H×16/17), 4.192 (q, *J*=7.1 Hz, 2H×1/17), 5.87—5.96 (m, 1H×1/17), 6.75 (tq, *J*=1.3, 7.4 Hz, 1H×16/17).

Ethyl (2*E*)- and (2*Z*)-8-(*t*-Butyldimethylsilyl)oxy-2-methyl-2-octenoate (11*E*) and 11*Z*). To a stirred solution of a mixture of **10*E*** and **10*Z*** (1.70 g, 8.49 mmol) in pyridine (20 ml) was added TBSCl (1.4 g, 9.3 mmol). After being stirred for 5 h, the solution was diluted with EtOAc (200 ml), and washed with 0.1 M aqueous HCl (100 ml), saturated aqueous $NaHCO_3$ (100 ml), and saturated brine (100 ml), successively. The organic layer was dried and concentrated in vacuo. The residue was purified by repeated column chromatography on silica gel (EtOAc/hexane, 1 : 80) and finally preparative thin-layer chromatography on silica gel (EtOAc/hexane, 1 : 30) to give 2.10 g (79%) of **11*E*** and 0.12 g (5%) of **11*Z***. Compound **11*E*** was obtained as a colorless oil: TLC, R_f 0.43 (EtOAc/hexane, 1 : 10); IR (neat) 1710, 1650 cm^{-1}; ^{1}H NMR (270 MHz) δ=0.05 (s, 6H), 0.89 (s, 9H), 1.29 (t, *J*=7.1 Hz, 3H), 1.32—1.59 (m, 6H), 1.80—1.85 (m, 3H), 2.12—2.23 (m, 2H), 3.60 (t, *J*=6.4 Hz, 2H), 4.18 (q, *J*=7.1 Hz, 2H), 6.75 (tq, *J*=1.5, 7.5 Hz, 1H). HRMS Calcd for $C_{17}H_{35}O_3Si$: (M^++H), *m/z* 315.2353. Found : *m/z* 315.2353. Compound **11*Z*** was obtained as a colorless oil: TLC, R_f 0.50 (EtOAc/hexane, 1 : 10); IR (neat) 1720, 1640 cm^{-1}; ^{1}H NMR (270 MHz) δ=0.04 (s, 6H), 0.89 (s, 9H), 1.30 (t, *J*=7.1 Hz, 3H), 1.31—1.58 (m, 6H), 1.89 (dd, *J*=1.5, 2.9 Hz, 3H), 2.39—2.50 (m, 2H), 3.60 (t, *J*=6.6 Hz, 2H), 4.19 (q, *J*=7.1 Hz, 2H), 5.92 (tq, *J*=1.5, 7.5 Hz, 1H). HRMS Calcd for $C_{17}H_{33}O_3Si$: (M^+−H), *m/z* 313.2197. Found : *m/z* 313.2185.

Ethyl (2*E*)-8-Hydroxy-2-methyl-2-octenoate (10*E*). To a cold (0 °C) stirred solution of **11*E*** (2.05 g, 6.52 mmol) in THF (20 ml) was added TBAF (1.0 M solution in THF, 8.2 ml, 8.2 mmol). After being stirred for 1 h, the solution was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 3) to give 1.21 g (93%) of **10*E*** as a colorless oil: TLC, R_f 0.58 (EtOAc/hexane, 1 : 1); IR (neat) 3400, 1715, 1650 cm^{-1}; ^{1}H NMR (270 MHz) δ=1.30 (t, *J*=7.1 Hz, 3H), 1.34—1.77 (m, 7H), 1.83 (d, *J*=1.5 Hz, 3H), 2.13—2.25 (m, 2H), 3.65 (t, *J*=6.4 Hz, 2H), 4.21 (q, *J*=7.1 Hz, 2H), 6.75 (tq, *J*=1.5, 7.5 Hz, 1H). HRMS Calcd for $C_{11}H_{20}O_3$: (M^+), *m/z* 200.1411. Found : *m/z* 200.1417. Found: C, 66.32, H, 10.02%. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07.

Mixture (20 : 1) of Ethyl (2*E* and *Z*, 5*R*)-5-(*t*-Butyldimethylsilyl)oxy-2-methyl-2-heptenoate (14*E* and 14*Z*). To a cold (0 °C) stirred suspension of PCC (5.50 g, 25.5 mmol) and powdered molecular sieves (4A, 2.4 g) in CH_2Cl_2 (50 ml) was added a solution of **12**[6] (3.67 g, 17.0 mmol) in CH_2Cl_2 (30 ml). After being stirred for 2.5 h, silica gel (5 g) and Et_2O (30 ml) were added to the mixture. The mixture was transferred to a short silica-gel column. The column was eluted with excess Et_2O to give 3.5 g of crude **13**, which was used in the next step without further purification, as a pale-yellow oil: TLC, R_f 0.60 (EtOAc/hexane, 1 : 5); ^{1}H NMR (90 MHz) δ=0.06, 0.08 (2s, 3H×2), 0.71—1.03 (m, 3H), 0.89 (s, 9H), 1.39—1.76 (m, 2H), 2.51 (dd, *J*=2.3, 5.6 Hz, 2H), 4.14 (quint, *J*=5.6 Hz, 1H), 9.82 (t, *J*=2.3 Hz, 1H).

To a stirred solution of crude **13** (3.5 g) in benzene (100 ml) was added Ph_3P=C(Me)CO_2Et (6.70 g, 18.5 mmol). The solution was refluxed for 1 h, and the solvent was removed by evaporation. The residue was triturated with excess petroleum ether, and the precipitated Ph_3P=O was removed by filtration and washed well with petroleum ether. The combined fitrate and washings were concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1 : 30) to give 3.86 g (76% from **12**) of an inseparable mixture of **14*E*** and **14*Z*** as a colorless oil (the ratio of the isomers, *E* : *Z*=ca. 20 : 1, was determined by ^{1}H NMR analysis). This product was unstable at r.t. on standing: TLC, R_f 0.44 (EtOAc/hexane, 1 : 30); IR (neat) 1710, 1650 cm^{-1}; ^{1}H NMR (270 MHz) δ=0.046, 0.049 (2 s, each 3H×20/21), 0.06 (s, 6H×1/21), 0.86—0.93 (m, 3H), 0.89 (s, 9H), 1.29 (t, *J*=7.1 Hz, 3H×20/21), 1.30 (t, *J*=7.1 Hz, 3H×1/21), 1.42—1.55 (m, 2H), 1.84 (d, *J*=1.1 Hz, 3H×20/21), 1.89—1.92 (m, 3H×1/21), 2.27—2.36 (m, 2H×20/21), 2.59—2.65 (m, 2H×1/21), 3.71 (quint, *J*=5.9 Hz, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 6.00—6.08 (m, 1H×1/21), 6.82 (tq, *J*=1.1 Hz, *J*=7.5 Hz, 1H×20/21).

Mixture (20 : 1) of (2*E* and *Z*, 5*R*)-5-(*t*-Butyldimethylsilyl)-oxy-2-methyl-2-heptenol (15*E* and 15*Z*). The following reaction was carried out under Ar. To a cold (−78 °C) stirred solution of the mixture of **14*E*** and **14*Z*** (3.80 g, 12.6 mmol) in CH_2Cl_2 (50 ml) was added Dibal-H (1.5 M solution in toluene, 20.0 ml, 30.0 mmol). After being stirred at −78 °C for 20 min, the solution was quenched with H_2O. The resulting gels were filtered off, and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 10) to give 2.65 g (81%) of an inseparable mixture of **15*E*** and **15*Z*** as a colorless oil: TLC, R_f 0.15 (EtOAc/hexane, 1 : 10); IR (neat) 3330 cm^{-1}; ^{1}H NMR (270 MHz) δ=0.04, 0.05 (2 s, each 3H×20/21), 0.08, 0.10 (2 s, each 3H×1/21), 0.88 (t, *J*=7.5 Hz, 3H), 0.89 (s, 9H×20/21), 0.90 (s, 9H×1/21), 1.32—1.63 (m, 3H), 1.67 (s, 3H×20/21), 1.79—1.82 (m, 3H×1/21), 2.15—2.24 (m, 2H), 3.62 (quint, *J*=6.0 Hz, 1H), 4.01 (s, 2H×20/21), 4.04 (s, 2H×1/21), 5.27—5.36 (m, 1H×1/21), 5.45 (tq, *J*=1.3 Hz, *J*=7.3 Hz, 1H×20/21). HRMS Calcd for $C_{14}H_{29}O_2Si$: (M^+−H), *m/z* 257.1934. Found : *m/z* 257.1929.

Mixture (20 : 1) of (2*E* and *Z*, 5*R*)-5-(*t*-Butyldimethylsilyl)oxy-1-chloro-2-methyl-2-heptene (16*E* and 16*Z*). To a stirred solution of a mixture of **15*E*** and **15*Z*** (2.65 g, 10.3 mmol) in CH_2Cl_2 (30 ml) were added Et_3N (7.2 ml, 52 mmol), Ph_3P (8.1 g, 31 mmol), and CCl_4 (3.0 ml, 31 mmol). After being stirred for 16.5 h, the solution was concentrated in vacuo. The residue was diluted with H_2O (200 ml) and extracted with Et_2O (150ml×2). The combined extracts were dried and concentrated in vacuo. The residue was triturated with excess petroleum ether, and the precipitated Ph_3P=O was removed by filtration and washed well with petroleum ether. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane, then petroleum ether/hexane, 1 : 10) to give 1.85 g (65%) of an inseparable mixture of **16*E*** and **16*Z*** as a colorless oil. This product was unstable at r.t. on standing: TLC, R_f 0.47 (hexane); ^{1}H NMR (270 MHz) δ=0.029 (s, 6H×1/21), 0.038, 0.042 (2 s, each 3H×20/21), 0.87 (t, *J*=7.3 Hz, 3H), 0.88 (s, 9H), 1.37—1.51 (m, 2H), 1.74 (d, *J*=1.1 Hz, 3H×20/21), 1.82—1.85 (m, 3H×1/21), 2.15—2.25 (m, 2H), 3.62 (quint, *J*=5.9 Hz, 1H×1/21), 3.63 (quint, *J*=5.9 Hz, 1H×20/21), 4.026, 4.029 (2 s, each 1H×20/21), 4.09, 4.13 (2 s, each 1H×1/21), 5.38—5.46 (m, 1H×1/21), 5.58 (dt, *J*=1.1, 7.3 Hz, 1H×20/21).

Mixture (20 : 1) of (2*E* and *Z*, 5*R*)-5-(*t*-Butyldimethylsilyl)oxy-2-methyl-2-hepten-1-yltriphenylphosphonium Chloride (17*E*

and 17Z). To the mixture of the allylic chlorides **16E** and **16Z** (1.85 g, 6.68 mmol) was added Ph_3P (1.86 g, 7.09 mmol), and the mixture was heated at 70—80 °C. After 3 d, the mixture was cooled to r.t. The resulting crystals were collected by filtration and washed well with Et_2O to give 2.62 g (73%) of an inseparable mixture of **17E** and **17Z** as white crystals, which were recrystallized from acetone/Et_2O (1 : 3), mp 175.0—176.0 °C, and used immediately for a Wittig reaction with **5**.

Mixture (2 : 1) of Ethyl (2E, 8E and Z, 10E, 13R)-13-(*t*-Butyldimethylsilyl)oxy-2,10-dimethyl-2,8,10-pentadecatrienoate (4E and 4Z). To a cold (0 °C) stirred suspension of powdered molecular sieves (4A, 1.7 g) and PCC (2.06 g, 9.56 mmol) in CH_2Cl_2 (20 ml) was added a solution of **10E** (950 mg, 4.74 mmol) in CH_2Cl_2 (20 ml). After being stirred for 1 h, the mixture was transferred to a short silica-gel column. The column was eluted with excess Et_2O to give 763 mg of crude **5**, which was used in the next step without further purification, as a pale-yellow oil: TLC, R_f 0.70 (EtOAc/hexane, 1 : 2); IR (neat) 1720, 1650 cm^{-1}; ^1H NMR (270 MHz) δ=1.30 (t, J=7.2 Hz, 3H), 1.37—1.74 (m, 4H), 1.80—1.86 (m, 3H), 2.14—2.26 (m, 2H), 2.46 (dt, J=1.7, 7.2 Hz, 2H), 4.19 (q, J=7.2 Hz, 2H), 6.73 (tq, J=1.5, 7.6 Hz, 1H), 9.77 (t, J=1.7 Hz, 1H).

The following reaction was carried out under Ar. To a cold (−17 °C) stirred suspension of a mixture of **17E** and **17Z** (20 : 1, 2.29 g, 4.25 mmol) in THF (20 ml) was added *n*-BuLi (1.6 M solution in hexane, 2.54 ml, 4.06 mmol). After being stirred for 20 min, a solution of crude **5** (763 mg) in THF (20 ml) was added. After being stirred for 20 min, the solution was quenched with saturated aqueous NH_4Cl and concentrated in vacuo. The residue was diluted with EtOAc (100 ml) and washed with H_2O (100 ml) and saturated brine (100 ml). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 60) to give 1.22 g (61% based on **10E**) of an inseparable mixture of **4E** and **4Z** as a colorless oil (the geometric ratio of the isomers, **4E** : **4Z**=ca. 2 : 1, was determined by ^1H NMR analysis): TLC, R_f 0.32 (EtOAc/hexane, 1 : 30); IR (neat) 1710, 1645 cm^{-1}; ^1H NMR (270 MHz) δ=0.04 (s, 6H), 0.87 (t, J=7.1 Hz, 3H), 0.89 (s, 9H), 1.29 (t, J=7.1 Hz, 3H), 1.45—1.55 (m, 6H), 1.72 (s, 3H×2/3), 1.76 (s, 3H×1/3), 1.82 (s, 3H), 2.02—2.35 (m, 6H), 3.56—3.68 (m, 1H), 4.19 (q, J=7.1 Hz, 2H), 5.21—5.43 (m, 1 H, 1H×1/3), 5.54 (dt, J=7.0 Hz, J=15.4 Hz, 1H×2/3), 5.81 (d, J=11.7 Hz, 1H×1/3), 6.06 (d, J=15.4 Hz, 1H×2/3), 6.75 (tq, J=1.5, 7.5 Hz, 1H). HRMS Calcd for $C_{25}H_{46}O_3Si$: (M^+), m/z 422.3213. Found : m/z 422.3187.

Intramolecular Diels–Alder Cycloaddition of the Mixture of 4E and 4Z. Ethyl (1S,2R,4aS,8aR)- (18), (1R,2S,4aR,8aS)- (19), (1S,2S,4aR,8aR)- (20), and (1R,2R,4aS,8aS)- (3) 2-[(*R*)-2-(*t*-Butyldimethylsilyl)oxy]butyl-1,3-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate. A mixture of **4E** and **4Z** (1.20 g, 2.84 mmol) was dissolved in toluene (25 ml), and the solution was divided into four 10 ml-sealed tubes with a screwed stopper. These four tubes were heated at 200 °C for 27 h. After being cooled to r.t., the combined solutions were concentrated in vacuo. The residue was purified by repeated column chromatography on silica gel (EtOAc/hexane, 1 : 100, then toluene/petroleum ether, 1 : 6) to give 178 mg (15%) of **18**, 170 mg (14%) of **19**, 298 mg (24%) of an inseparable mixture of **20** and **3**, and 282 mg of **21** which was contained by ca. 10% of the mixture of unreacted **4E** and **4Z**.

Compound **18** was obtained as a colorless oil: TLC, R_f 0.55 (EtOAc/hexane, 1 : 30); $[\alpha]_D^{21}$ −30.6° (*c* 1.10, $CHCl_3$); IR (neat) 1720 cm^{-1}; ^1H NMR (270 MHz) δ=0.04, 0.09 (2s, 3H×2), 0.86 (t, J=7.3 Hz, 3H), 0.89 (s, 9H), 1.10 (s, 3H), 1.27 (t, J=7.1 Hz, 3H), 1.30—1.86 (m, 15H), 1.71 (s, 3H), 3.42—3.51 (m, 1H), 3.97—4.09 (m, 1H), 4.13—4.24 (m, 1H), 5.06 (s, 1H). HRMS Calcd for $C_{25}H_{47}O_3Si$: (M^++H), m/z 423.3292. Found : m/z 423.3308.

Compound **19** was obtained as a colorless oil: TLC, R_f 0.45 (EtOAc/hexane, 1 : 30); $[\alpha]_D^{21}$+40.5° (*c* 0.22, $CHCl_3$); IR (neat) 1720, 1680 cm^{-1}; ^1H NMR (270 MHz) δ=0.02, 0.07 (2s, 3H×2), 0.83 (t, J=7.5 Hz, 3H), 0.89 (s, 9H), 1.11 (s, 3H), 1.21—1.82 (m, 14H), 1.29 (t, J=7.1 Hz, 3H), 1.68 (s, 3H), 1.89—1.96 (m, 1H), 3.23 (ddt, J=1.8, 4.5, 9.0 Hz, 1H), 3.97—4.18 (m, 2H), 5.05 (s, 1H). HRMS Calcd for $C_{25}H_{46}O_3Si$: (M^+), m/z 422.3213. Found : m/z 422.3212.

A mixture of **20** and **3** was obtained as a colorless oil (the ratio of **20** and **3** was determined to be ca. 1 : 1 by ^1H NMR analysis): TLC, R_f 0.42 (EtOAc/hexane, 1 : 30), IR (neat) 1720 cm^{-1}; ^1H NMR (270 MHz) δ=0.057, 0.069, 0.091, 0.095 (4s, each 3H×1/2), 0.87 (t, J=7.5 Hz, 3H×1/2), 0.88 (s, 9H×1/2), 0.90 (t, J=7.3 Hz, 3H×1/2), 0.91 (s, 9H×1/2), 1.10—1.72 (m, 12H), 1.21, 1.22 (2t, J=7.1 Hz, each 3H×1/2), 1.23, 1.26 (2s, each 3H×1/2), 1.72—1.81 (m, 3H), 1.89—2.02, 2.16—2.27, 2.55—2.69 (3 m, 1H×3), 3.48—3.57, 3.57—3.67 (2 m, each 1H×1/2), 3.98—4.20 (m, 2H), 4.96, 4.99 (2s, each 1H×1/2). HRMS Calcd for $C_{25}H_{46}O_3Si$: (M^+), m/z 422.3213. Found : m/z 422.3188.

Compound **21**, which was purified by repeated column chromatography on silica gel for spectral analysis, was obtained as a colorless oil: TLC, R_f 0.47 (EtOAc/hexane, 1 : 10); IR (neat) 1710, 1650 cm^{-1}; ^1H NMR (270 MHz) δ=0.056, 0.058 (2s, 3H×2), 0.88—0.90 (m, 3H), 0.91 (s, 9H), 1.30 (t, J=7.2 Hz, 3H), 1.44—1.55 (m, 6H), 1.75 (s, 3H), 1.82 (d, J=1.1 Hz, 3H), 2.07—2.29 (m, 6H), 3.60 (quint, J=5.7 Hz, 1H), 4.29 (q, J=7.2 Hz, 2H), 5.52 (dt, J=7.1, 15.0 Hz, 1H), 5.77 (d, J=10.6 Hz, 1H), 6.24 (dd, J=10.6, 15.0 Hz, 1H), 6.75 (tq, J=7.3, 1.1 Hz, 1H). HRMS Calcd for $C_{25}H_{47}O_3Si$: (M^++H), m/z 423.3291. Found : m/z 423.3277.

(1S,2R,4aS,8aR)-2-[(*R*)-2-Hydroxybutyl]-1,3-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylic Acid 1,2′-Lactone (22). To a stirred solution of **18** (23.0 mg, 0.054 mmol) in DMSO (1 ml) was added *t*-BuOK (37.7 mg, 0.34 mmol); the solution was heated at 60 °C for 2 h and then cooled to r.t. The solution was acidified with 1 M aqueous HCl (pH 3). After being stirred for 14 h, the solution was diluted with Et_2O (20 ml) and washed with H_2O (10ml×3). The combined aqueous layers were extracted with Et_2O (10 ml). The combined ethereal layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 20) to give 13.1 mg (92%) of **22** as a colorless oil: TLC, R_f 0.33 (EtOAc/hexane, 1 : 10); $[\alpha]_D^{20}$+107.3° (*c* 0.32, $CHCl_3$); IR (neat) 1725 cm^{-1}; ^1H NMR (270 MHz) δ=1.00 (t, J=7.3 Hz, 3H), 1.06—1.87 (m, 13H), 1.16 (s, 3H), 1.71 (s, 3H), 1.97—2.09 (m, 2H), 4.16 (ddt, J=2.7, 6.0, 9.0 Hz, 1H), 5.19 (s, 1H). HRMS Calcd for $C_{17}H_{26}O_2$: (M^+), m/z 262.1931. Found : m/z 262.1917.

(1R,2S,4aR,8aS)-2-[(*R*)-2-Hydroxybutyl]-1,3-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylic Acid (23). To a stirred solution of **19** (24.2 mg, 0.057 mmol) in DMSO (1 ml) was added *t*-BuOK (33.3 mg, 0.30 mmol); the solution was then heated at 60 °C for 3 h. The solution was acidified with 1 M aqueous HCl (pH 3). After being stirred for 1.5 h, the solution was diluted with Et_2O (15 ml), and washed with H_2O (10ml×3). The combined aqueous layers were extracted with Et_2O (20 ml). The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/toluene, 1 : 4) to give 15.0 mg (94%) of **23** as white amorphous solids: TLC, R_f 0.43 (EtOAc/toluene, 1 : 1); mp 124—126 °C; $[\alpha]_D^{21}$+39.9° (*c* 0.38, $CHCl_3$); IR (KBr disk) 3509, 1709, 1697 cm^{-1}; ^1H NMR (270 MHz) δ=0.91 (t, J=7.5 Hz, 3H), 0.98—1.85 (m, 14H), 1.15

(s, 3H), 1.71 (s, 3H), 1.87—2.00, 2.02—2.11 (2m, 1H×2), 3.32—3.46 (m, 1H), 5.12 (s, 1H). HRMS Calcd for $C_{17}H_{29}O_3$: (M^++H), *m/z* 281.2115. Found : *m/z* 281.2106.

(1*R*,2*S*,4a*R*,8a*S*)-2-[(*R*)-2-Hydroxybutyl]-1,3-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylic Acid 1,2′-Lacotne (24). To a stirred solution of **19** (20.9 mg, 0.049 mmol) in DMSO (1.5 ml) was added *t*-BuOK (27.7 mg, 0.25 mmol); the solution was then heated at 60 °C for 2 h. The solution was acidified with 1 M aqueous HCl (pH 2). After being stirred at 40 °C for 16.5 h, the solution was diluted with Et_2O (20 ml), and washed with H_2O (10ml×3). The combined aqueous layers were extracted with Et_2O (20 ml). The ethereal layers were combined, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 30) to give 10.1 mg (78%) of **24** as a colorless oil: TLC, R_f 0.38 (EtOAc/hexane, 1 : 10); $[\alpha]_D^{24}$ −56.8° (*c* 0.55, $CHCl_3$); IR (neat) 1730 cm^{-1}; ^1H NMR (270 MHz) δ=1.00 (t, *J*=7.3 Hz, 3H), 1.05—2.00 (m, 14H), 1.12 (s, 3H), 1.70 (s, 3H), 2.08—2.18 (m, 1H), 4.40—4.52 (m, 1H), 5.25 (s, 1H). HRMS Calcd for $C_{17}H_{26}O_2$: (M^+), *m/z* 262.1930. Found : *m/z* 262.1923.

(1*S*,2*S*,4a*R*,8a*R*)- (25) and (1*R*,2*R*,4a*S*,8a*S*)- (1) 2-[(*R*)-2-Hydroxybutyl]-1,3-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylic Acid. To a stirred solution of a mixture of **20** and **3** (89.4 mg, 0.21 mmol) in DMSO (3 ml) was added *t*-BuOK (144 mg, 1.28 mmol); the solution was then heated at 60 °C for 4 h. The solution was acidified with 1 M aqueous HCl (pH 3). After being stirred for 2.5 h, the solution was diluted with Et_2O (35 ml), and washed with H_2O (15ml×3). The ethereal layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/toluene, 1 : 4) to give 14.7 mg (25%) of **25**, 16.7 mg (28%) of **1**, and 25.0 mg (28%) of the mixture of **25** and **1**.

Compound **25** was obtained as a colorless oil: TLC, R_f 0.48 (EtOAc/toluene, 1 : 1); $[\alpha]_D^{21}$+91.5° (*c* 0.22, $CHCl_3$); IR (neat) 3380, 1695 cm^{-1}; ^1H NMR (270 MHz) δ=0.96 (t, *J*=7.3 Hz, 3H), 1.04—1.84 (m, 13H), 1.30 (s, 3H), 1.78 (d, *J*=0.7 Hz, 3H), 1.94—2.04, 2.33—2.44, 2.58—2.68 (3m, 1H×3), 2.38 (br, 1H), 2.64 (br, 1H), 3.45 (tt, *J*=4.1, 8.2 Hz, 1H), 5.06 (s, 1H). HRMS Calcd for $C_{17}H_{27}O_3$: (M^+−H), *m/z* 279.1958. Found : *m/z* 279.1986.

Compound **1** was obtained as white crystals: TLC, R_f 0.40 (EtOAc/toluene, 1 : 1); mp 137.0—139.0 °C; $[\alpha]_D^{25}$ −84.2° (*c* 0.11, $CHCl_3$); IR (neat) 3400, 1695 cm^{-1}; ^1H NMR (270 MHz) δ=0.97 (t, *J*=7.3 Hz, 3H), 1.17—1.71 (m, 13H), 1.33 (s, 3H), 1.74 (s, 3H), 1.96—2.06 (m, 1H), 2.33—2.45 (m, 1H), 2.57—2.65 (m, 1H), 3.53 (tt, *J*=4.2, 8.3 Hz, 1H), 5.04 (s, 1H). HRMS Calcd for $C_{17}H_{26}O_2$: (M^+-H_2O), *m/z* 262.1931. Found : *m/z* 262.1920.

(1*S*,2*S*,4a*R*,8a*R*)-2-[(*R*)-2-Hydroxybutyl]-1,3-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylic Acid 1,2′-Lacotne (26). To a stirred solution of **25** (14.7 mg, 0.052 mmol) in benzene (1 ml) was added *p*-TsOH·H_2O (27.7 mg, 0.15 mmol). After being stirred for 3.5 h, the mixture was diluted with saturated aqueous $NaHCO_3$ (10 ml), and extracted with CH_2Cl_2 (15ml×3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 30) to give 10.6 mg (77%) of **26** as a colorless oil: TLC, R_f 0.32 (EtOAc/hexane, 1 : 10); $[\alpha]_D^{27}$ −30.4° (*c* 0.19, $CHCl_3$); IR (neat) 1730 cm^{-1}; ^1H NMR (270MHz) δ=1.09 (t, *J*=7.1 Hz, 3H), 1.16 (s, 3H), 1.35—1.92 (m, 10H), 1.70 (dt, *J*=1.5, 2.2 Hz, 3H), 1.97—2.07 (m, 1H), 2.09 (dt, *J*=8.4, 13.6 Hz, 1H), 2.13—2.30, 2.31—2.41, 2.44—2.57 (3 m, 1H×3), 4.43—4.55 (m, 1H), 5.44—5.51 (m, 1H). HRMS Calcd for $C_{17}H_{26}O_2$: (M^+), *m/z* 262.1930. Found : *m/z* 262.1913.

(1*S*,2*R*,4a*S*,8a*R*)-2-[(*R*)-2-Hydroxybutyl]-1-hydroxymethyl-1,3-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene (27). To a cold (0 °C) stirred suspension of $LiAlH_4$ (5.0 mg, 0.13 mmol) in THF (1 ml) was added a solution of **22** (13.1 mg, 0.050 mmol) in THF (1.5 ml). $LiAlH_4$ (4.4 mg, 0.12 mmol) was added to the mixture after 20 min. After being stirred for an additional 20 min, the mixture was quenched with H_2O, diluted with 1 M aqueous HCl (15 ml), and extracted with EtOAc (20ml×3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/toluene, 1 : 6) to give 12.8 mg (96%) of **27** as a colorless oil: TLC, R_f 0.57 (EtOAc/toluene, 1 : 1); $[\alpha]_D^{24}$ −64.9° (*c* 0.64, $CHCl_3$); IR (neat) 3270 cm^{-1}; ^1H NMR (270 MHz) δ=0.84—1.81 (m, 13H), 0.93 (s, 3H), 0.95 (t, *J*=7.3 Hz, 3H), 1.49 (quint., *J*=7.3 Hz, 2H), 1.69 (s, 3H), 3.05 (br, 2H), 3.38, 3.66 (ABq, *J*=11.5 Hz, 1H×2), 3.65—3.76 (m, 1H), 4.99 (s, 1H). HRMS Calcd for $C_{17}H_{28}O$: (M^+-H_2O), *m/z* 248.2138. Found : *m/z* 248.2132.

(1*S*,2*R*,4a*S*,8a*R*)-1-[(*t*-Butyldimethylsilyl)oxy]methyl-2-[(*R*)-2-hydroxybutyl]-1,3-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene (28). To a stirred solution of **27** (13.1 mg, 0.049 mmol) in CH_2Cl_2 (1 ml) were added Et_3N (0.021 ml, 0.15 mmol), 4-dimethylaminopyridine (DMAP) (6.4 mg, 0.052 mmol), and TBSCl (11.9 mg, 0.079 mmol). While after 2.5, 4.5, and 6 h, each 13.3 mg, 7.5 mg, and 3.3 mg of TBSCl was added to the mixture. After being stirred for an additional 1.5 h, the solution was diluted with saturated aqueous $NaHCO_3$ (15 ml), and extracted with CH_2Cl_2 (20ml×3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 60) to give 16.2 mg (87%) of **28** as a colorless oil: TLC, R_f 0.57 (EtOAc/hexane, 1 : 10); $[\alpha]_D^{23}$ −42.1° (*c* 0.81, $CHCl_3$); IR (neat) 3470 cm^{-1}; ^1H NMR (270 MHz) δ=0.09, 0.10 (2s, 3H×2), 0.85 (s, 3H), 0.86—1.84 (m, 18H), 0.93 (s, 9H), 1.71 (s, 3H), 3.48, 3.66 (ABq, *J*=10.3 Hz, 1H×2), 3.59—3.72 (m, 2H), 5.00 (s, 1H). HRMS Calcd for $C_{23}H_{45}O_2Si$: (M^++H), *m/z* 381.3186. Found : *m/z* 381.3175.

(1*S*,2*R*,4a*S*,8a*R*)-1-[(*t*-Butyldimethylsilyl)oxy]methyl-1,3-dimethyl-2-(2-oxobutyl)-1,2,4a,5,6,7,8,8a-octahydronaphthalene (29). To a stirred solution of **28** (8.7 mg, 0.023 mmol) in CH_2Cl_2 (1 ml) were added powdered molecular sieves (4A, 19.9 mg) and PDC (16.6 mg, 0.044 mmol). After being stirred for 3 h, the mixture was transferred to a short silica-gel column. The column was eluted with excess Et_2O, and the ethereal eluates were concentrated in vacuo. The residue was purified by column chromatography on silica gel (toluene/petroleum ether, 1 : 3) to give 8.3 mg (96%) of **29** as a colorless oil: TLC, R_f 0.52 (EtOAc/hexane, 1 : 15); $[\alpha]_D^{22}$ −2.9° (*c* 0.42, $CHCl_3$); IR (neat) 1720 cm^{-1}; ^1H NMR (270 MHz) δ=0.016, 0.019 (2s, 3H×2), 0.79 (s, 3H), 0.84—1.82 (m, 10H), 0.89 (s, 9H), 1.06 (t, *J*=7.3 Hz, 3H), 1.56 (s, 3H), 2.24 (dd, *J*=5.9, 17.2 Hz, 1H), 2.39 (dd, *J*=5.9, 7.4 Hz, 1H), 2.45 (q, *J*=7.3 Hz, 2H), 3.04 (dd, *J*=7.4, 17.2 Hz, 1H), 3.42 (s, 2H), 5.08 (s, 1H). HRMS Calcd for $C_{23}H_{42}O_2Si$: (M^+), *m/z* 378.2952. Found : *m/z* 378.2986.

(1*R*,2*S*,4a*R*,8a*S*)-2-[(*R*)-2-Hydroxybutyl]-1-hydroxymethyl-1,3-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene (30). To a cold (0 °C) stirred suspension of $LiAlH_4$ (5.9 mg, 0.16 mmol) in THF (1 ml) was added a solution of **24** (10.1 mg, 0.039 mmol) in THF (1 ml). After being stirred for 45 min, the mixture was refluxed for 35 min. The mixture was quenched with H_2O, diluted with H_2O (15 ml), and extracted with EtOAc (15ml×3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/toluene, 1 : 6) to give 10.1 mg (98%) of **30** as a colorless oil: TLC, R_f 0.57 (EtOAc/toluene, 1 : 1); $[\alpha]_D^{22}$ −18.9° (*c* 0.52, $CHCl_3$); IR (neat) 3390 cm^{-1}; ^1H NMR (270 MHz) δ=0.87 (s, 3H), 0.92—1.93 (m,

15H), 0.97 (t, J=7.5 Hz, 3H), 1.68 (s, 3H), 2.43—2.52 (m, 2H), 3.50, 3.56 (ABq, J=11.0 Hz, 1H×2), 3.73 (d of quint., J=3.0, 12.1 Hz, 1H), 5.10 (s, 1H). HRMS Calcd for $C_{17}H_{29}O_2$: (M^+-H), m/z 265.2166. Found : m/z 265.2180.

(1*R*,2*S*,4a*R*,8a*S*)-1-[(*t*-Butyldimethylsilyl)oxy]methyl-2-[(*R*)-2-hydroxybutyl]-1,3-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene (31). To a stirred solution of **30** (10.4 mg, 0.039 mmol) in CH_2Cl_2 (1 ml) were added DMAP (5.0 mg, 0.041 mmol), Et_3N (16.5 ml, 0.12 mmol), and TBSCl (8.0 mg, 0.053 mmol). The solution was stirred for 24.5 h, while TBSCl (31.9 mg, 0.21 mmol), Et_3N (5.0 ml, 0.036 mmol), and DMAP (2.8 mg, 0.023 mmol) were added for completion of the silylation. The solution was diluted with saturated aqueous $NaHCO_3$ (10 ml), and extracted with CH_2Cl_2 (15ml×3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 60) to give 13.2 mg (89%) of **31** as a colorless oil: TLC, R_f 0.58 (EtOAc/touene, 1 : 10); $[\alpha]_D^{24}$+33.3° (c 0.23, $CHCl_3$); IR (neat) 3475 cm^{-1}; ^1H NMR (270 MHz) δ=0.07, 0.08 (2s, 3H×2), 0.82 (s, 3H), 0.92 (s, 9H), 0.96 (t, J=7.3 Hz, 3H), 1.00—1.89 (m, 15H), 1.69 (s, 3H), 2.41 (br, 1H), 3.46, 3.50 (2 ABq, J=13.2 Hz, 1H×2), 3.63—3.76 (m, 1H), 5.07 (s, 1H). HRMS Calcd for $C_{23}H_{45}O_2Si$: (M^++H), m/z 381.3187. Found : m/z 381.3238.

(1*R*,2*S*,4a*R*,8a*S*)-1-[(*t*-Butyldimethylsilyl)oxy]methyl-1,3-dimethyl-2-(2-oxobutyl)-1,2,4a,5,6,7,8,8a-octahydronaphthalene (32). To a cold (0 °C) stirred solution of **31** (9.0 mg, 0.024 mmol) in CH_2Cl_2 (1 ml) were added powdered molecular sieves (4A, 5.3 mg) and PDC (10.1 mg, 0.027 mmol). After being stirred for 3.5 h, PDC (3.5 mg, 9.3 mmol) was added to the mixture. The mixture was then stirred for an additional 40 min, and PDC (2.8 mg, 7.4 mmol) was added. After being stirred for an additional 40 min, the mixture was transferred to a short silica-gel column. The column was eluted with excess Et_2O, and the eluate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (toluene/petroleum ether, 1 : 2) to give 7.2 mg (80%) of **32** as a colorless oil: $[\alpha]_D^{24}$+3.5° (c 0.36, $CHCl_3$). IR and ^1H NMR (270 MHz) were completely identical to those for **29**. HRMS Calcd for $C_{23}H_{42}O_2Si$: (M^+), m/z 378.2952. Found : m/z 378.2956.

Mixture of Ethyl (1*S*,2*S*,4a*R*,8a*R*)- (33), (1*R*,2*R*,4a*S*,8a*S*)- (34) 2-[(*R*)-2-Hydroxybutyl]-1,3-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate. To a stirred solution of mixture of **20** and **3** (13.6 mg, 0.032 mmol) in 50% aqueous THF (0.4 ml) was added AcOH (0.6 ml). After being stirred for 60 h, the solution was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 10) to give 9.1 mg (95%) of an inseparable mixture of **33** and **34** as a colorless oil: TLC, R_f 0.28 (EtOAc/hexane, 1 : 5); IR (neat) 3480, 1725 cm^{-1}; ^1H NMR (270 MHz) δ=0.96 (t, J=7.3 Hz, 3H×1/2), 0.97 (t, J=7.3 Hz, 3H×1/2), 1.10—1.71 (m, 13H), 1.23 (s, 3H×1/2), 1.24 (t, J=7.3 Hz, 3H), 1.27 (s, 3H×1/2), 1.71—1.82 (m, 3H), 1.94—2.05 (m, 1H), 2.16—2.27 (m, 1H), 2.59—2.71 (m, 1H), 3.37—3.59 (m, 1H), 4.02—4.22 (m, 2H), 5.00—5.08 (m, 1H).

Racemic Mixture (1 : 1) of Enantiomers, Ethyl (1*S*,2*S*,4a*R*, 8a*R*)- (35), (1*R*,2*R*,4a*S*,8a*S*)- (36) 1,3-Dimethyl-2-(2-oxobutyl)-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate. To a cold (0 °C) stirred solution of a mixture of **33** and **34** (9.1 mg, 0.030 mmol) in CH_2Cl_2 (1 ml) were added powdered molecular sieves (4A, 31.7 mg) and PDC (34.0 mg, 0.090 mmol). After being stirred for 1 h, the mixture was transferred to a short silica-gel column. The column was eluted with excess Et_2O, and the eluate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 30) to give 7.6 mg (84%) of a racemic mixture of **35** and **36** as a colorless oil: TLC, R_f 0.54 (EtOAc/hexane, 1 : 5); IR (neat) 1720 cm^{-1}; ^1H NMR (270 MHz) δ=1.08 (t, J=7.3 Hz, 3H), 1.11 (s, 3H), 1.14—1.61 (m, 7H), 1.61—1.66 (m, 3H), 1.66—1.73 (m, 1H), 1.22 (t, J=7.1 Hz, 3H), 1.94—2.05 (m, 1H), 2.17—2.27 (br, 1H), 2.41 (dd, J=5.1, 18.3 Hz, 1H), 2.45 (q, J=7.3 Hz, 2H), 2.65 (dd, J=5.7, 18.3 Hz, 1H), 3.43—3.51 (m, 1H), 4.02—4.21 (m, 2H), 5.07 (brs, 1H). HRMS Calcd for $C_{19}H_{30}O_3$: (M^+), m/z 306.2195. Found : m/z 306.2214.

Mixture (2 : 1) of (2*E*,8*E* and *Z*,10*E*,13*R*)-13-(*t*-Butyldimethylsilyl)oxy-2,10-dimethyl-2,8,10-pentadecatrien-1-ol (37). The following reaction was carried out under Ar. To a cold (−78 °C) stirred solution of mixture of **4*E*** and **4*Z*** (138 mg, 0.33 mmol) in CH_2Cl_2 (3 ml) was added Dibal-H (1.01 M solution in toluene, 0.98 ml, 0.99 mmol). After being stirred for 1 h, the solution was quenched with H_2O. The resulting gels were filtered off and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 20) to give 112 mg (90%) of a 2 : 1 inseparable mixture **37** as a colorless oil (the ratio of the (*E*)- and (*Z*)-isomers was determined based on the ^1H NMR analysis): TLC, R_f 0.41 (EtOAc/hexane, 1 : 5); IR (neat) 3310 cm^{-1}; ^1H NMR (270 MHz) δ=0.038, 0.043 (2s, each 3H), 0.82—0.93 (m, 3H), 0.89 (s, 9H), 1.23—1.56 (m, 7H), 1.66 (s, 3H×2/3), 1.72 (s, 3H×1/3), 1.76 (s, 3H), 1.97—2.34 (m, 6H), 3.62 (quint, J=5.8 Hz, 1H), 4.00 (d, J=5.1 Hz, 2H), 5.29 (dt, J=7.3, 11.7 Hz, 1H×1/3), 5.32—5.47 (m, 2H), 5.57 (dt, J=7.0, 15.6 Hz, 1H×2/3), 5.78 (d, J=11.7 Hz, 1H×1/3), 6.02 (d, J=15.6 Hz, 1H×2/3). HRMS Calcd for $C_{19}H_{35}O_2Si$: ($M^+-C_4H_9$), m/z 323.2404. Found : m/z 323.2373.

Mixture (2 : 1) of (2*E*,8*E* and *Z*,10*E*,13*R*)-13-(*t*-Butyldimethylsilyl)oxy-2,10-dimethyl-2,8,10-pentadecatrienal (38). To a stirred solution of mixture **37** (112 mg, 0.30 mmol) in CH_2Cl_2 (5 ml) was added $BaMnO_4$ (1.14 g, 4.43 mmol). After being stirred for 5 h, the insoluble materials were filtered off and washed well with CH_2Cl_2. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (toluene/petroleum ether, 1 : 3; then EtOAc/hexane, 1 : 80) to give 102 mg (92%) of an inseparable mixture **38** as a colorless oil: TLC, R_f 0.68 (EtOAc/hexane, 1 : 5); IR (neat) 1690, 1645 cm^{-1}; ^1H NMR (270 MHz) δ=0.034, 0.040 (2s, each 3H), 0.82—0.95 (m, 3H), 0.89 (s, 9H), 1.34—1.58 (m, 6H), 1.72 (s, 3H×1/3), 1.74 (s, 3H×2/3), 1.75 (s, 3H), 2.06—2.43 (m, 6H), 3.62 (q, J=5.7 Hz, 1H), 5.28 (dt, J=7.3, 11.7 Hz, 1H×1/3), 5.40 (q, J=7.3 Hz, 1H), 5.56 (dt, J=6.8, 15.6 Hz, 1H×2/3), 5.81 (d, J=11.7 Hz, 1H×1/3), 6.04 (d, J=15.6 Hz, 1H×2/3), 6.43—6.55 (m, 1H), 9.40 (s, 1H). HRMS Calcd for $C_{23}H_{41}O_2Si$: (M^+-H), m/z 377.2874. Found : m/z 377.2874.

Intramolecular Diels–Alder Cycloaddition of the Mixture 38. Mixture of (1*S*,2*R*,4a*S*,8a*R*)-, (1*R*,2*S*,4a*R*,8a*S*)-, (1*R*,2*R*,4a*S*, 8a*S*)-, and (1*S*,2*S*,4a*R*,8a*R*)-2-[(*R*)-2-[(*t*-Butyldimethylsilyl)oxy]-butyl]-1,3-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde (39). To a cold (−18 °C) stirred solution of the mixture **38** (21.0 mg, 0.055 mmol) in CH_2Cl_2 (3 ml) was added Et_2AlCl (0.97 M solution in hexane, 0.17 ml, 0.16 mmol). After being stirred for 4.5 h at −18 °C, the solution was quenched with H_2O. The solution was diluted with saturated brine (20 ml) and extracted with CH_2Cl_2 (20ml×3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (toluene/petroleum ether, 1 : 5) to give 10.5 mg (50%) of an inseparable mixture **39** as a colorless oil (the diastereomeric ratio of isomers, ca. 10 : 10 : 1 : 1, was determined by ^1H NMR analysis), and 6.0 mg (29%) of unreacted (*Z*)-isomer **38*Z*** was recovered. The inseparable mixture **39**: TLC, R_f

0.73 (petroleum ether/toluene, 1 : 1); IR (neat) 1725 cm^{-1}; ^1H NMR (270 MHz) δ=0.007—0.096 (m, 6H×1/11), 0.025 (s, 6H×5/11), 0.051, 0.069 (each s, each 3H×5/11), 0.81—0.93 (m, 3H×1/11 and 9H×1/11), 0.84 (t, J=7.6 Hz, 3H×5/11), 0.86 (t, J=7.3 Hz, 3H×5/11), 0.88, 0.89 (2 s, each 9H×5/11), 0.99, 1.00 (2 s, each 3H×5/11), 1.02—1.05 (m, 3H×1/11), 1.23—1.99 (m, 15H and 3H×1/11), 1.67, 1.69 (2 s, each 3H×5/11), 3.35 (ddt, J=2.1, 4.2, 6.3 Hz, 1H×5/11), 3.46—3.72 (m, 1H×6/11), 4.97—5.05 (m, 1H×1/11), 5.10, 5.13.(2s, each 1H×5/11), 9.35, 9.37 (2s, each 1H×1/22), 9.61, 9.63 (2s, each 1H×5/11). HRMS Calcd for $C_{23}H_{42}O_2Si$: (M^+), m/z 378.2951. Found : m/z 378.2931. The recovered **38Z**: TLC, R_f 0.34 (EtOAc/hexane, 1 : 15); IR (neat) 1690 1645 cm^{-1}; ^1H NMR (270 MHz) δ=0.034, 0.040 (2s, 3H×2); 0.74—1.03 (m, 3H), 0.89 (s, 9H), 1.16—1.93 (m, 6H), 1.72 (s, 3H), 1.75 (s, 3H), 1.94—2.53 (m, 6H), 3.62 (q, J=5.6 Hz, 1H), 5.28 (dt, J=7.3, 11.7 Hz, 1H), 5.40 (q, J=7.3 Hz, 1H), 5.81 (d, J=11.7 Hz, 1H), 6.41—6.59 (m, 1H), 9.40 (s, 1H).

(1*S*,2*R*,4a*S*,8a*R*)- (40) and (1*R*,2*S*,4a*R*,8a*S*)- (41) 2-[(*R*)-2-[(*t*-Butyldimethylsilyl)oxy]butyl]-1-hydroxymethyl-1,3-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene. To a cold (0 °C) stirred solution of mixture **39** (5.6 mg, 0.015 mmol) in THF (1 ml) was added $LiAlH_4$ (0.6 mg, 1.6 μmol). The mixture was stirred at r.t. for 25 min, and quenched with H_2O. The insoluble materials were filtered off and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 100) to give 2.0 mg (36%) of **40** and 2.1 mg (38%) of **41**.

Compound **40** was obtained as a colorless oil: TLC, R_f 0.61 (EtOAc/hexane, 1 : 10); $[\alpha]_D^{22}$+59.9° (c 0.14, $CHCl_3$); IR (neat) 3460, 1735 cm^{-1}; ^1H NMR (270 MHz) δ=0.13, 0.16 (2s, each 3H); 0.88 (t, J=7.6 Hz, 3H), 0.91 (s, 3H), 0.94 (s, 9H), 0.98—1.84 (m, 15H), 1.72 (s, 3H), 3.32 (t, J=12.5 Hz, 1H), 3.61—3.69 (m, 1H), 3.64 (dd, J=2.0, 12.5 Hz, 1H), 3.80—3.93 (m, 1H), 5.03 (s, 1H).

Compound **41** was obtained as a colorless oil: TLC, R_f 0.45 (EtOAc/hexane, 1 : 10); $[\alpha]_D^{22}$+30.1° (c 0.20, $CHCl_3$);IR (neat) 3450 cm^{-1}; ^1H NMR (270 MHz) δ=0.08, 0.10 (2 s, each 3H), 0.85 (s, 3H), 0.86—0.97 (m, 3H), 0.91 (s, 9H), 0.97—1.95 (m, 16H), 1.68 (s, 3H), 3.49 (s, 2H), 3.87 (ddt, J=3.3, 5.5, 8.1 Hz, 1H), 5.03 (s, 1H).

(1*S*,2*R*,4a*S*,8a*R*)-2-[(*R*)-2-Hydroxybutyl]-1-hydroxymethyl-1,3-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene (27) from 40. To a stirred solution of **40** (2.5 mg, 0.0066 mmol) in THF (0.2 ml) were added H_2O (0.2 ml) and AcOH (0.6 ml). After being stirred for 14 h, the mixture was concentrated with aid of toluene and EtOH in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 5) to give 1.5 mg (88%) of **27** as a colorless oil.

(1*R*,2*S*,4a*R*,8a*S*)-2-[(*R*)-2-Hydroxybutyl]-1-hydroxymethyl-1,3-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene (30) from 41. To a stirred solution of **41** (5.6 mg, 0.015 mmol) in THF (0.2 ml) were added H_2O (0.2 ml) and AcOH (0.6 ml). After being stirred for 23 h, the solution was concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 5) to give 3.3 mg (85%) of **30** as a colorless oil.

Ethyl (2*E* and *Z*)-8-(*t*-Butyldimethylsilyl)oxy-2-octenoate (43*E* and 43*Z*). The following reaction was carried out under Ar. To a cold (−78 °C) stirred solution of **7** (304 mg, 2.67 mmol) in CH_2Cl_2 (6 ml) was added Dibal-H (1.01 M solution in toluene, 2.8 ml, 2.8 mmol) dropwise over 35 min. After being stirred at −78 °C for 1 h, the mixture was quenched with H_2O. The solids were filtered off and washed well with EtOAc. The combined filtrate and washings were concentrated in vacuo to give 304 mg of crude **9**, which was used in the next step.

To a stirred solution of crude **9** (304 mg) in benzene (15 ml) was added Ph_3P=$CHCO_2Et$ (1.41 g, 4.43 mmol). The solution was refluxed for 1.5 h and concentration in vacuo. The residue was triturated with excess petroleum ether, and the precipitated Ph_3P=O was removed by filtration and washed well with petroleum ether. The filtrate and washings were combined and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 3) to give 362 mg of an inseparable mixture of **42*E*** and **42*Z***, which was used in the next step.

To a stirred solution of the mixture of **42*E*** and **42*Z*** (362 mg) in pyridine (8 ml) was added TBSCl (425 mg, 2.82 mmol). After being stirred for 17 h, the solution was diluted with saturated brine (90 ml) and extracted with EtOAc (100ml×3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 60) to give 399 mg (50% from **7**) of **43*E*** and 24.7 mg (3% from **7**) of **43*Z***.

Compound **43*E*** as a colorless oil: TLC, R_f 0.50 (EtOAc/hexane, 1 : 15); IR (neat) 1725, 1655 cm^{-1}; ^1H NMR (270 MHz) δ=0.04 (s, 6H), 0.89 (s, 9H), 1.23—1.59 (m, 6H), 1.29 (t, J=7.0 Hz, 3H), 2.20 (dq, J=1.5, 7.0 Hz, 2H), 3.60 (t, J=6.4 Hz, 2H), 4.18 (q, J=7.0 Hz, 2H), 5.81 (dt, J=1.5 15.8 Hz, 1H), 6.96 (dt, J=7.0 15.8 Hz, 1H). HRMS Calcd for $C_{15}H_{29}O_3Si$: (M^+−Me), m/z 285.1883. Found : m/z 285.1874.

Compound **43*Z*** as a colorless oil: TLC, R_f 0.57 (EtOAc/hexane, 1 : 15); IR (neat) 1720, 1645 cm^{-1}; ^1H NMR (270 MHz) δ=0.04 (s, 6H), 0.89 (s, 9H), 1.29 (t, J=7.1 Hz, 3H), 1.32—1.61 (m, 6H), 2.59—2.72 (m, 2H), 3.60 (t, J=6.4 Hz, 2H), 4.16 (q, J=7.1 Hz, 2H), 5.75 (dt, J=1.8, 11.4 Hz, 1H), 6.21 (dt, J=7.5 11.4 Hz, 1H). HRMS Calcd for $C_{15}H_{29}O_3Si$: (M^+−Me), m/z 285.1883. Found : m/z 285.1874.

Ethyl (2*E*)-8-Hydroxy-2-octenoate (42*E*). To a stirred solution of **43*E*** (399 mg, 1.33 mmol) in THF (2 ml) were added H_2O (2 ml) and AcOH (2 ml). After being stirred for 2.5 h, the solution was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 3) to give 245 mg (99%) of **42*E*** as a colorless oil: TLC, R_f 0.47 (EtOAc/hexane, 1 : 15); IR (neat) 3420, 1720, 1655 cm^{-1}; ^1H NMR (270 MHz) δ=1.29 (t, J=7.1 Hz, 3H), 1.33—1.65 (m, 6H), 1.80 (br, 1H), 2.23 (dq, J=1.5, 7.0 Hz, 2H), 3.64 (t, J=6.4 Hz, 2H), 4.18 (q, J=7.1 Hz, 2H), 5.82 (dt, J=1.5, 15.5 Hz, 1H), 6.96 (dt, J=7.0, 15.5 Hz, 1H).

Mixture (2 : 1) of Ethyl (2*E*,8*E* and *Z*,10*E*,13*R*)-13-(*t*-Butyldimethylsilyl)oxy-10-methyl-2,8,10-pentadecatrienoate (45). To a cold (0 °C) stirred solution of **42*E*** (20.5 mg, 0.11 mmol) in CH_2Cl_2 (1 ml) were added powdered molecular sieves (4A, 42.2 mg) and PCC (49.5 mg, 0.20 mmol). After being stirred for 1 h, Et_2O (1 ml) and silica gel (0.4 g) were added to the mixture. The mixture was transferred to a short silica-gel column. The column was eluted with excess Et_2O to give 17.9 mg of crude **44**, which was used in the next step without further purification, as a pale-yellow oil: TLC, R_f 0.68 (EtOAc/hexane, 1 : 2).

The following reaction was carried out under Ar. To a cold (0 °C) stirred suspension of **17*E*** (121 mg, 0.22 mmol) in THF (1 ml) was added *n*-BuLi (1.66 M solution in hexane, 0.12 ml, 0.20 mmol). After being stirred for 30 min, a solution of crude **44** (17.9 mg) in THF (1.5 ml) was added. After being stirred for 15 min, the solution was quenched with saturated aqueous NH_4Cl, diluted with saturated brine (20 ml), and extracted with EtOAc (25ml×3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1 : 100) to give 26.3 mg (58%) of

an inseparable mixture **45** as a colorless oil (the geometric ratio of the isomers, **45*E*** : **45*Z***=ca. 2 : 1, was based on the ^{1}H NMR analysis): TLC, R_f 0.51 (EtOAc/hexane, 1 : 10); IR (neat) 1715, 1655 cm^{-1}; ^{1}H NMR (270 MHz) δ=0.02—0.06 (m, 6H), 0.85—0.92 (m, 3H×1/3), 0.87 (t, J=7.3 Hz, 3H×2/3), 0.89 (s, 9H), 1.29 (t, J=7.1 Hz, 3H), 1.34—1.55 (m, 6H), 1.72 (br, 3H×2/3), 1.75 (br, 3H×1/3), 2.04—2.31 (m, 6H), 3.56—3.68 (m, 1H), 4.18 (q, J=7.1 Hz, 2H), 5.25 (dt, J=7.2, 11.9 Hz, 1H×1/3), 5.31—5.44 (m, 1H), 5.52 (dt, J=7.0, 15.4 Hz, 1H×2/3), 5.77—5.86 (m, 1H×1/3), 5.81 (dt, J=1.5, 15.4 Hz, 1H), 6.05 (d, J=15.4 Hz, 1H×2/3), 6.96 (dt, J=7.0, 15.4 Hz, 1H). HRMS Calcd for $C_{24}H_{45}O_3Si$: (M^++H), m/z 409.3136. Found : m/z 409.3146.

Intramolecular Diels–Alder Cycloaddition of the Mixture 45. Mixture of Ethyl (1*S*,2*R*,4a*S*,8a*R*)-, (1*R*,2*S*,4a*R*,8a*S*)-, (1*S*,2*S*,4a*R*,8a*R*)-, and (1*R*,2*R*,4a*S*,8a*S*)-2-[(*R*)-2-(*t*-Butyldimethylsilyl)-oxy]butyl-3-methyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (46). After a mixture **45** (26.3 mg, 0.064 mmol) was dissolved in toluene (1 ml), the solution was heated at 160 °C for 21 h in a sealed tube. Then, after being cooled to r.t., the solvent was removed by concentration in vacuo. The residue was purified by column chromatography on silica gel (toluene/petroleum ether, 1 : 6 then EtOAc/hexane, 1 : 80) to give 15.7 mg (60%) of an inseparable mixture **46** as a colorless oil (the diastereomeric ratio of the isomers, ca. 2 : 2 : 1 : 1, was determined by ^{1}H NMR analysis): TLC, R_f 0.51 (EtOAc/hexane, 1 : 10); IR (neat) 1715 cm^{-1}; ^{1}H NMR (270 MHz) δ=0.02 (s, 6H×1/6), 0.05 (s, 6H×2/3), 0.10 (s, 6H×1/6), 0.81—0.91 (m, 3H), 0.88, 0.89 (2 s, each 9H×1/2), 1.23—2.09 (m, 20H), 2.23—2.37, 2.39—2.53, 2.57—2.67, (3 m, total 2H), 3.21—3.33 (m, 1H×1/3), 3.45—3.56, (m, 1H×1/3), 3.57—3.67 (m, 1H×1/6), 3.66—3.76 (m, 1H×1/6), 3.94—4.25 (m, 2H), 5.09 (s, 1H×2/3), 5.33—5.43 (m, 1H×1/3). HRMS Calcd for $C_{24}H_{43}O_3Si$: (M^+−H), m/z 407.2979. Found : m/z 407.2977.

We are grateful to the staff of the Applied Biology Laboratories, Taisho Pharmaceutical Co., Ltd. for donating a sample and spectra of **1** and useful information. We are also indebted to Dr. Tadashi Nakata (RIKEN) for the loan of a high-pressure reaction equipment. The Biochemical Research Laboratories of Kaneka Ltd. is also appreciated for the gift of **8**.

References

1) Y. Kishimura, A. Kawashima, T. Kagamizono, M. Yamagishi, K. Matsumoto, Y. Kawashima, and K. Hanada, *J. Antibiot.*, **45**, 892 (1992).

2) Compound **1** lactonizes gradually to **2** in a $CDCl_3$ solution; personal communication from Dr. A. Kawashima (Taisho Pharmaceutical Co., Ltd.)

3) Total synthesis of **1** was reported in a preliminary communication form: K. Tadano, T. Murata, T. Kumagai, and S. Ogawa, *Tetrahedron Lett.*, **34**, 7279 (1993).

4) A relevant recent review on this subject, see: W. R. Roush, "Stereoselective and Synthetic Studies of the Intramolecular Diels–Alder Reaction," in "Advances in Cycloaddition," ed by D. P. Curran, JAI Press, Greenwich (1990), Vol. 2, p. 91.

5) Our starting material **8** was communicated to possess $[\alpha]_D^{20}$ −35.3° (*c* 1, $CHCl_3$). Judging from the reported value for enantiomerically pure **8** $[\alpha]_D^{22}$ −36.9° (*c* 1.31, $CHCl_3$), our sample was estimated to be more than 95% ee. See: K. Mori and H. Watanabe, *Tetrahedron*, **41**, 3423 (1985).

6) K. Mori and H. Kishida, *Tetrahedron*, **42**, 5281 (1986).

7) F. C. Chang and N. F. Wood, *Tetrahedron Lett.*, **1964**, 2969.

8) W. R. Roush, "Intramolecular Diels–Alder Reactions, " in "Comprehensive Organic Synthesis," ed by B. M. Trost, I. Fleming, and L. A. Paquette, Pergamon Press, Oxford (1991), Vol. 5, p. 513, and references cited therein.